REMARKS

Claims 284-529 were previously pending in this application. Claims 284, 331-332, 337, 348, 376-377, 381, 385-386, 390-392, 513-518, 522-524 and 526 have been amended. New claims 530-568 have been added and no claims have been canceled by this paper. Accordingly, claims 284-568 are presented for further examination.

Applicants' undersigned attorney would like to thank Examiner Marschel for the time and courtesy that was extended at the interview held on August 3, 1999. It is believed that the discussions at the interview have helped considerably in resolving any remaining issues in this application. As a followup to the August 3rd interview and in a sincere effort to define their claimed invention more particularly, thereby rendering it in a better condition for allowance, Applicants have effected a number of amendments to the specification and the pending claims.

Specification Amendments

The specification has been amended on pages 93 and 98 by the insertion of disclosure taken from the originally filed claims. The originally filed claims included several dependent claims directed to specific base labeling positions involving the so-called non-Ward (U.S. Patent No. 4,711,955)[1] as well as other dependent claims directed to the embodiments

[1] The originally filed claims to specific base labeling positions included the following:

12. A nucleotide in accordance with Claim 1 wherein said base B is a pyrimidine and wherein said Sig chemical moiety is attached to the pyrimidine at the N3 position.

15. A nucleotide in accordance with Claim 1, wherein said base B is a pyrimidine and wherein said Sig chemical moiety is attached to the pyrimidine at the C6 position.

16. A nucleotide in accordance with Claim 1 wherein said base B is a purine and wherein said Sig chemical moiety is attached to the purine at the N1 position.

17. A nucleotide in accordance with Claim 1 wherein said base B is a purine and wherein said Sig chemical moiety is attached to the purine at the C2 position.

for the Sig detectable moiety.[2] As discussed in further detail in the next section which follows below, several dependent claims based directly on the language of the originally filed claims have been added as new claims.

Claim Amendments

Several amendments to the pending claims, many involving informalities and minor errors, have been made above as follows.

First, the designations for various base positions in the claims have been corrected in accordance with conventional usage. The affected claims include claims 284, 331, 332, 337, 348, 376, 381, 385, 390 and 522-524. That is to say, the superscripts for various ring positions in the purine and pyrimidine bases have been removed and replaced with normal characters. This applies, for example, to the attachment of the furanose moiety SM to the N1 position when BASE is a pyrimidine and the N9 position when BASE is a purine. Also affected are the recited "other than" positions, including the C5 position when BASE is a pyrimdine, the C8 position when BASE is a pyrimidine, and the C7 when BASE is a 7-deazapurine. With respect to claim 523, an extraneous semicolon and conjunction (and) has been deleted and replaced with a proper period (.).

Footnote 1 (continued)

18. A nucleotide in accordance with Claim 1 wherein said base B is a purine and wherein said Sig chemical moiety is attached to the purine at the N3 position.

20. A nucleotide in accordance with Claim 1 wherein said base B is a purine and wherein said Sig chemical moiety is attached to the purine at the N7 position.

[2] The originally filed claims to embodiments for the Sig detectable moiety included the following:

11. A nucleotide in accordance with Claim 1 wherein said Sig chemical moiety is an aliphatic chemical moiety containing at least 4 carbon atoms.

13. A nucleotide in accordance with Claim 1 wherein said Sig chemical moiety is an aliphatic chemical moiety containing at least 3 carbon atoms and at least one double bond.

19. A nucleotide in accordance with Claim 1 wherein said base B is a purine and wherein said Sig chemical moiety contains an aromatic or a cycloaliphatic group containing at least six or at least five carbon atoms.

Second, in the claimed chromosomal characterization processes, further amendments have been made to several claims, including 376-377, 381, 385-386 and 390-392. In claim 376, the first step is now defined as "contacting said cell under hybridizing conditions with one or more clones or DNA fragments or oligo- or polynucleotides derived from said clone or clones, each of which is capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, said clones or DNA fragments or oligo- or polynucleotides comprising at least one modified nucleotide selected from . . ." In the last part of the first contacting step as well as the second detecting step of claim 376, reference is also now made to the "clone or clones or DNA fragments or oligo- or polynucleotides." Similarly, claim 377 which depends from 376, now refers to "said one or more clones or DNA fragments or oligo- or polynucleotides [as being] derived from said particular chromosome."

Reference to a set of "clones or DNA fragments or oligo- or polynucleotides derived from said clone or clones has also been incorporated into claim 381 which is a process for identifying a chromosome of interest in a cell containing other chromosomes. Such reference has been made to the first providing step, the third contacting step and the fourth detecting step in claim 381. The same changes as in just-described claim 381 have been made to claim 385, that claim being directed to a process for identifying a plurality or all of the chromosomes in a cell of interest. The changes in claim 385 have been made to the first providing step, the third contacting step and the last detecting step. Claim 386 depends from claim 385 and it also now refers to the "set of clones or DNA fragments or oligo- or polynucleotides [being] labeled with the same indicator molecule."

Also among the chromosomal characterization claims is claim 390 which is directed to a process for determining the number of chromosomes in an interphase cell of interest. As amended above, the first step in claim 390 calls for "providing sets of clones or DNA fragments or oligo- or polynucleotides derived from said clones, each of said set of clones or DNA fragments or oligo- or polynucleotides being specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest and each of said clones or DNA fragments or

oligo- or polynucleotides in said sets comprising at least one modified nucleotide selected from . . ." Similar reference to the "clones or DNA fragments or oligo- or polynucleotides derived from said clones" is made in the second contacting step and third detecting step of claim 390. Lastly, claims 391 and 392, both of which depend from claim 390, now define the embodiment wherein each of said sets of clones or DNA fragments or oligo- or polynucleotides is labeled with the same indicator molecule [claim 391] or a different indicator molecule [claim 392].

Referring to the phrase "clones or DNA fragments or oligonucleotides or polynucleotides" which is incorporated into various chromosomal characterization claims and process steps, it is believed that this language is proper under U.S. patent practice as an acceptable form of claiming using alternative expressions. The elements, clones, DNA fragments and oligo- or polynucleotides, are basically equivalents for the purpose of the invention and these elements claimed alternatively do not introduce any uncertainty or ambiguity with respect to the scope or breadth of the chromosomal characterization claims. For example, Oliver and Ward [A Dictionary of Genetic Engineering, Cambridge University Press, Cambridge & London, 1985] define the term "clone" thusly:

> **clone** This term is used in a number of senses. As a noun, it may mean (i) a population of recombinant DNA molecules all carrying the same inserted sequence, or (ii) a population of cells or organisms of identical genotype. It is most frequently used to describe a colony of microorganisms which harbour a ***specific DNA fragment*** inserted into a vector molecule.
>
> As a verb 'to clone' means to use *in vitro* recombination techniques to insert a particular gene or other ***DNA sequence*** into a vector molecule.
>
> [A Dictionary of Genetic Engineering, page 18, emphasis added]

A copy of Oliver & Ward's definition is attached to this paper as Exhibit A.

Finally, in §2173.05(h) **Alternative Expressions** of the Manual of Patent Examining Procedure (MPEP) under *(b) "Or" terminology*, the following is written:

> Alternative expressions using "or" are acceptable, such as "wherein R is A, B, C, or D." The following phrases were each held to be acceptable and not in violation of 35 U.S.C. 112, second paragraph in *In re Gaubert*, 524 F.2d 1222, 187 USPQ 664 (CCPA 1975): "made entirely or in part of", "at least one piece", and "iron, steel or any other magnetic material."
>
> [MPEP, Rev. July 3, 1997, page 2100-168]

Third, relatively minor amendments have also been made to claims 513-518 and 526, which refer to either seven pathogenic bacteria (claims 513-516) or *Neisseria gonorrhoeae* (claims 517-518 and 526). These now define the nucleic acid of interest or the oligo- or polynucleotides as being *derived* from the Markush group of pathogenic bacteria or *Neisseria gonorrhoeae* itself.

It is believed that no new matter has been inserted by any of the above amendments to the claims. In many instances, these amendments conform the language to conventional usage or serve to clarify that which is being claimed by the Applicants. Entry of the above claim amendments is respectfully requested.

New Claims

New claims 530-568 have been added above. In claim 530 which depends from four independent sequencing claims previously presented, a phosphate modified nucleotide is recited. This nucleotide mimics the third Markush nucleotide designated as nucleotide (iii) in claims 331 and 522.

Dependent embodiments have been added for the Sig detectable moiety in the hybridization detection processes, the sequencing processes and the preparation process. In the detection processes, for example, claims 531-534 have been added, the support for which is taken from originally filed claims 11, 13 and 19 recited in footnote 2 above. In the dependent process claims 535 and 536, also for detection, specific base labeling positions are recited. Thus, claim 535 recites the C2, the N3 and the C6 position when BASE is a pyrimidine, and the N1, the C2, the N3, the C6 and the N7 position when BASE is a purine. These positions are taken again

from the originally filed claims, this time, claims 12, 15, 16, 17, 18 and 20, which are recited in footnote 1 above. As also indicated in the opening remarks of this paper, disclosure directed to the originally filed claims recited in footnotes 1 and 2 has been added to pages 93 and 98 in the specification. Lastly, with respect to the detection process claims, new claim 536 is directed to the covalent attachment in nucleotide (i) of the Sig detectable moiety to the BASE "at a position selected from the group consisting of the N^4 position when said pyrimidine comprises cytosine, the N^2 position when said purine comprises adenine or deazaadenine, the N^6 position when said purine comprises guanine or deazaguanine, and combinations thereof." Support for claim 536 is taken from the specification, page 95, last paragraph. See also originally filed claim 142.

The rest of the newly added claims 537-568 track claims 531-536. Thus, sequencing claims 537-539 and 541 follow claims 531-534, respectively. It should be pointed out that claims 540 and 542 depend from the aforementioned claims 539 and 541, respectively. Both claims 540 and 542 recite "wherein said aromatic or cycloaliphatic group is fluorescent or chemiluminescent." It is believed that the specification is replete with support in which the Sig detectable moiety comprises fluorescent or chemiluminescent components, and that no further elaboration need be made here. Two other sequencing claims, 543 and 544, are directed to the specific base labeling positions recited in claims 535 and 536, discussed *supra*. A similar pattern has been made for claims 553-560, which ultimately depend from sequencing claim 548, as well as for claims 561-568, which ultimately depend from sequencing claim 522 (and ultimately, claims 520 or 521).

A similar pattern exists for the dependent claims 545-552 added above for Applicants' claimed preparation process (ultimately claim 337).

Entry of claims 530-568 is respectfully requested.

Base Modifications

In the August 3, 1999 Examiner Interview Summary Record, it was indicated that "We discussed whether there was, and of what scope, the support for base modifications at other than Ward [modification] positions. The new matter [rejections] in the action mailed 1/6/98, are deemed overcome."

As discussed above, the non-Ward base modification positions were disclosed in originally filed claims 12, 15, 16, 17, 18 and 20 (recited in footnote 1 above). Further elaboration of these positions was made in Applicants' May 1, 1999 Fourth Supplemental Amendment. See pages 48, through the first paragraph on page 51 of that paper. See also Exhibits 5-16 referenced on pages 48-50.

Chromosomal Characterization Process Claims

Claims 376-395 are directed to various processes for chromosomal characterization. These claims are further divided into:

determining whether the number of copies of a particular chromosome in a cell is normal or abnormal	claims 376-380
identifying a chromosome of interest in a cell containing other chromosomes	claims 381-384
identifying a plurality or all of the chromosomes in a cell of interest	claims 385-389
determining the number of chromosomes in an interphase cell of interest	claims 390-392

With respect to these so-called "chromosomal" claims (376-392), it is believed that the subject matter of these claims is fully supported and described in the originally filed specification.

Determination of Chromosomal Copy Number - Normal/Abnormal (Claims 376-380)

Support for claims 376-380 is found in Part II (Diagnosis of Genetic Disorders) of Example 9 (Uses of Labeled DNA Sequences), where there is disclosed on pages 47-48:

> By selecting the clones which bind specifically to a particular chromosome, such as number 23, it is possible to count the number of copies of the particular chromosome in a cell even if the chromosomes are not condensed in metaphase. If necessary, two sets of labels can be used--one which would be specific for chromosomes 23 and one for some other chromsome. By measuring in each cell the ratio of the two labels, which might be of different colors, it is possible to identify the cells which show an abnormal number of chromosome number 23. This procedure could be used either on slides with a low-light-level video system or in a flow cytometer system using laser excitation. It can be used to determine any abnormal chromosome number.
>
> [underline added]

The foregoing passage fully supports the subject matter of claim 376. Concerning claim 377 and its recitation that "said one or more clones or DNA fragments or oligo- or polynucleotides are derived from said particular chromosome," this language is supported by the disclosure beginning on page 47, last line, and continuing through the first two lines on page 48 ("By selecting the clones which bind specifically to a particular chromosome, such as number 23, it is possible to count the number of copies . . ."). See also page 46, last three lines, and continuing through page 47, line 3 ("For those clones which correspond to a unique sequence gene this determines the location of the cloned DNA on a particular human chromosome. Obtain several clones for such chromosome. Each of these labeled clones can be used to identify particular chromosomes").

Claims 378-380 depend from claim 376 and recite embodiments for the detection step of the latter. Claim 378 recites "wherein said detecting step is carried out by a means selected from the group consisting of manual means and automatic means." Support for the foregoing language is found in the specification, page 47, lines 15-16 ("These labels could be used for visual or computerized automatic karyotyping"). See also the last four lines before the section titled II (Diagnosis of Genetic Disorders) ("By using the fact that the fluorescent spots can be placed at specific locations on each

chromosome one can carry out either manual or automatic karyotyping very much more effectively than without such labels"). The disclosure just quoted also supports the subject matter of claims 379 ("manual means comprises visualization") and 380 ("automatic means comprises computerized automatic karyotyping").

Identifying Chromosome of Interest in Cell Containing Other Chromosomes (Claims 381-384)

Support for claims 381-384 is found in Example 9 (Uses of Labeled DNA Sequences) under I Karyotyping on pages 46-47. There, it is disclosed:

> (a) Select from a human gene library some 100 to 200 clones. Label them as described above, and for each clone locate its place or places of hybridization visually or with a low-light-level video system. For those clones which correspond to a unique sequence gene this determines the location of the cloned DNA on a particular human chromosome. Obtain several clones for each chromosome. Each of these labeled clones can be used to identify particular chromosomes . . . These labels could be used for visual or computerized automatic karyotyping. [underline added]

Identifying Plurality/All Chromosomes in Cell of Interest (Claims 385-389)

Support for the subject matter of claims 385-389 is also taken from the passage last quoted above. In the quotation indicated as being deleted, it is disclosed:

> They [labeled clones] can also be used in combination to identify each of the 46 chromosomes as being one of the 22 autosomal pairs or the X or the Y. By allowing one set of labeled clones to hybridize to the chromosome and then adding a fluorescent stain to the label, the set of clones and their locations can be visualized and will flouresce(sic) with a particular color. A second set of labeled clones could then be used and reacted with a second fluorescent dye. The same process can be repeated a number of times. Thus one can, if desired, have several sets of fluorescent labels attached to the cellular DNA at different but specific locations on each of the chromosomes. These labels could be used for visual or computerized automatic karyotyping. [underline added]

Determining Number of Chromosomes in Interphase Cell (Claims 390-392)

Support for the subject matter of claims 390-395, each of which is directed to a process for determining the number of chromosomes in an interphase cell of interest, is also found in Example 9, II Diagnosis of Genetic Disorders. Beginning with the last line on page 47 and continuing into page 48, it is disclosed:

> By selecting the clones which bind specifically to a particular chromosome, such as number 23, it is possible to count the number of copies of the particular chromosome in a cell even if the chromosomes are not condensed at metaphase. Thus when fetal cells are obtained for prenatal diagnosis of trisomy 21, the diagnosis can be done even if the chromosomes are not condensed at metaphase. If necessary, two sets of labels can be used--one which would be specific for chromosome 23 and one for some other chromosome. By measuring in each cell the ratio of the two labels, which might be of different colors, it is possible to identify the cells which show an abnormal number of chromsome number 23. This procedure could be used either on slides with a low-light-level video system or in a flow cytometer system using laser excitation. It can be used to determine any abnormal chromosome number. [underline added]

In addition to supporting independent claim 390, the above-quoted passage also supports claims 391 and 392, which are directed the sets of clones being labeled with the same indicator molecule (claim 391) or with a different indicator molecule (claim 392). See underlined portions regarding "two sets of labels" and "different colors." Support for claims 393-395 follows that of claims 378-380, 382-384 and 387-389.

Thus, it is quite clear that the original specification, largely in the form of Example 9 (Uses of Labeled DNA Sequences) supports and fully describes the subject matter of claims 376-395.

Favorable action on the pending claims is respectfully requested.

* * * * * * *

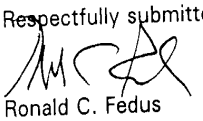
SUMMARY AND CONCLUSIONS

Claims 284-529 were previously pending in this application. Claims 284, 331-332, 337, 348, 376-377, 381, 385-386, 390-392, 513-518, 522-524 and 526 have been amended. New claims 530-568 have been added and no claims have been canceled by this paper. Accordingly, claims 284-568 are presented for further examination.

The claim fee for adding new claims 530-568 is $702 based upon the large entity fee of $18 for each additional new claim (39 new claims X $18 = $702). The Patent and Trademark Office is authorized to charge the $702 claim fee to Deposit Account No. 05-1135. No other fee or fees are believed due in connection with filing this Eighth Supplemental Amendment. In the event that any other such fee or fees are due, however, authorization is hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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